

REMARKS

Claims 97 and 157 through 175 are under examination in the application.

Claims 97 and 157 through 165 were objected to for assertedly being substantially identical.

Claims 97 and 157 through 175 were rejected under 35 USC 103(a) for being directed to subject matter assertedly rendered obvious by various combinations of references.

Prior to addressing the examiner's concerns, the applicant would first like to be certain that the nature of the invention is made clear.

The present invention

The present invention is recited in two embodiments in the claims. In the first embodiment (as broadly recited in claim 97), microchips are provided upon which oligonucleotides are arrayed. The microchips are themselves arrayed and immobilized on a support. The microchips are characterized by having different oligonucleotides attached, and the microchips are separated from each other on the support by a physical barrier or a hydrophobic surface. In the second embodiment (as broadly recited in claim 166), a support is provided upon which microarrays of oligonucleotide are themselves arrayed. As with the first embodiment, the individual microarrays are separated from each other on the support by a physical barrier or a hydrophobic surface. The two embodiments differ in that in the second embodiment, the microarrays are attached directly on the underlying support, whereas in the first embodiment, the oligonucleotide arrays are immobilized on microchips, and the microchips are immobilized on the underlying support.

The utility of the invention is evident in the specification. By separating the microchips or individual microarrays, distinct spatial areas are created on the support (see page 16, lines 35-37 in the application as filed) thereby permitting parallel execution of large numbers of distinct reactions on a single support (see page 42, lines 9-11). The specification acknowledges that grid-like positioning on a filter, wherein individual regions on the membrane are separated from each other, was known in the art at the time the instant

invention was made. See page 40, line 27, through page 42, line 5. However, even with this knowledge in the art, it was only in the instant invention that separation of microarrays of oligonucleotides or microchips having oligonucleotides attached was demonstrated, thereby allowing for the parallel hybridization of heretofore unachieved and exceptionally large numbers of reactions.

This invention has revolutionized the research and clinical worlds, allowing for the accumulation of data at a previously unimagined rate. Even today, the full potential of this powerful invention has not been realized.

Microarray technology evolved from Southern blotting, where fragmented DNA is attached to a substrate and then probed with a known gene or fragment. The use of a collection of distinct DNAs in arrays for expression profiling was first described in 1987, and the arrayed DNAs were used to identify genes whose expression is modulated by interferon.[Kulesh et al., (1987). Proc Natl Acad Sci USA 84 (23): 8453–8457] These early gene arrays were made by spotting cDNAs onto filter paper with a pin-spotting device. The use of miniaturized microarrays for gene expression profiling was first reported in 1995, [Schena, et al., Science 270 (5235): 467–470] and a complete eukaryotic genome (*Saccharomyces cerevisiae*) on a microarray was published in 1997. [Lashkari, et al., (1997) Proc Natl Acad Sci USA 94 (24): 13057–13062]
(http://en.wikipedia.org/wiki/DNA_microarray)

Fischer, Pharmacogenomics (2003) 4(4), 379-381, confirms this history.

Since their introduction in the mid-1990s [citation omitted], microarrays have become the paradigm for comprehensive, highthroughput expression analysis and, for the first time, promised to 'get the whole picture' of the transcriptome, overriding the severe throughput problems inherent to earlier methods such as subtractive hybridization or differential display. Meanwhile, many companies offer solutions and products related to this technology, and thousands of scientific publications have been published reporting results obtained by the use of microarrays

Thus, the importance of the present invention and its practical use is well understood even today. Moreover, the potential for its exploitation has now been fully realized.

Claim objection

At pages 2-3 of the office action, the examiner set out the following objection to the claims.

Applicant is advised that should claims 97 and 157-165 be found allowable, claims 166-175 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim 166 has been amended to define an array of microarrays. Claim 97 is drawn to an array of microchips. Applicant points to the specification for support of the newly claimed "microarrays". The cited passages describe arrays of oligonucleotides on microchips. From this, Applicant is equating microarrays and microchips. It is acknowledged that "microarray" and "microchip" are both used currently to describe probes immobilized on a surface at high-density. Therefore, Claims 97 and 166 cover the same subject matter. The claim sets differ only in that Claim 97 defined the oligonucleotides as attached "at different locations". While Claim 166 does not include this recitation, oligonucleotides are inherently attached at different locations. By definition, attachment requires an attachment site. Hence, it is impossible to attach any two oligonucleotides to the exact same location. Therefore, despite a slight difference in wording, Claims 166-175 cover the same subject matter as Claims 97 and 157-165.

The applicant respectfully disagrees.

As discussed above, the invention is claimed in two broad embodiments. In the first embodiment (as broadly recited in claim 97), microchips are provided upon which oligonucleotides are arrayed. The microchips are themselves arrayed and immobilized on a

support. The microchips are characterized by having different oligonucleotides attached, and the microchips are separated on the support from each other by a physical barrier or a hydrophobic surface. In the second embodiment (as broadly recited in claim 166), a support is provided upon which microarrays of oligonucleotide are themselves arrayed. As with the first embodiment above, the individual microarrays are separated from each other on the support by a physical barrier or a hydrophobic surface. The two embodiments differ in that in the second embodiment, the microarrays are directly on the underlying support, whereas in the first embodiment, the oligonucleotide arrays are supported on microchips, and the microchips are immobilized on the underlying support.

Despite the subtle difference, the two embodiments of the invention as set out in claims 97 and 166 are distinct. In one aspect, oligonucleotide are immobilized directly on a support, and in another aspect, oligonucleotides are immobilized on microchips which are, in turn, immobilized on a support. Accordingly, the objection to the claims must be withdrawn.

The first rejection under 35 USC 103(a)

Claims 97 and 157 through 175 were rejected under 35 U.S.C. 103(a) as being assertedly rendered obvious by the disclosure of Southern et al (Genomics, 1992, 13: 1008-1017, hereinafter "Southern") in view of the disclosure of Brigati (U.S. Patent No. 4,777,020, hereinafter "Brigati") or the disclosure of Augenlicht (U.S. Patent No. 4,981,783, hereinafter "Augenlicht"). The examiner's position is set out below

Regarding Claims 97, 157-158 and 166-168, Southern discloses a support comprising an array of four microchips, each having an array of oligonucleotide probes immobilized thereon (Fig. 3, figure legend, line 1).

Southern teaches each array is in one of four quadrants on the surface (Fig. 3). The four-quadrant arrangement is encompassed by the physical separation because a quadrant defines a physical location of the surface. Assignment of an array to a quadrant defines a boundary between quadrants, the boundary being the point of physical separation. While the reference specifically teaches that the arrays are physically separated, Southern does not specifically teach a physical barrier. However, physical and hydrophobic barriers separating

hybridization regions were well known and routinely practiced in the art at the time the instant invention was made as taught by Brigati who teaches that the groove and hydrophobic barriers provide for comparative analysis of hybridization to the same probes to different samples and/or hybridization of different probes to the same sample (Column 9, line 63-Column 10, line 15).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the physical separation of Brigati to the multiple arrays of Southern. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success and for the benefit of comparative analysis of the multiple arrays to different samples as desired in the art (Brigati, Column 9, line 63- Column 10, line 15).

The applicant disagrees.

Several points must be addressed with respect to comments made by the examiner in the office action.

Regarding the examiner's assertion that "Southern discloses a support comprising an array of four **microchips**, each having an array of oligonucleotide probes immobilized thereon (Fig. 3, figure legend, line 1)" (emphasis added), the applicant submits that this position is an overstatement of what Southern actually says. The legend to Fig. 3 actually states, "The plate carries **four copies of an array** of all 256 octapurines, one in each of the four quadrants." (Emphasis added.) Thus, Fig. 3 provides an arrangement of four **arrays, not microchips**, of oligonucleotides.

Regarding the examiner's comment that "[t]he four-quadrant arrangement is encompassed by the physical separation because a quadrant defines a physical location of the surface," the applicant submits that this position is irrelevant. "Physical **separation**" standing alone is not a limitation of the pending claims; claims 97 and 166 recite "separated by a physical barrier or hydrophobic surface." This point is made clear by the examiner's subsequent admission that "Southern does not specifically teach a physical barrier." The applicant notes that Southern also does not teach the alternative "hydrophobic surface."

Despite the examiner's admission that the Southern reference does not teach that the individual arrays in the Figure 3 arrangement are separated by physical or hydrophobic barriers, the examiner continues with the rejection alleging that physical and

hydrophobic barriers were well known and routinely practiced in the art at the time the instant invention was made, as purportedly evidenced by the disclosure of Brigati. With this position stated, the examiner concluded that one of ordinary skill in the art would have been motivated to separate the Southern arrays as disclosed in Brigati with a reasonable expectation of success and for the benefit of comparative analysis of the multiple arrays to different samples as desired in the art.

This position overlooks the important contribution the invention makes to the art.

As discussed above, the present invention provides the previously unrealized advantage of performing parallel and distinct hybridization reactions, i.e., oligonucleotides in each array separated by the recited physical barrier or hydrophobic surface are or can be hybridized to different targets, and the combined disclosures of Southern and Brigati do not disclose or suggest such a possibility.

Even though the examiner asserts that the four arrays described in Southern are "physically separated," the disclosure offers no suggestion that separate hybridization reactions can be carried out with four different arrays on the membrane. Brigati fails to correct this deficiency.

The examiner makes reference to the disclosure in Brigati at column 9, line 63 to column 10, line 15, which states,

It should be appreciated that a single sample can be simultaneously assayed for antibodies against different antigens, if these antigens are pre-bound as spots in a known pattern on strips 623 and 643. Alternatively, identical spots can be formed on strips 623 and 643 to be exposed to the same serum sample and washed. The slides can then be removed from the holder and rearranged in different slide pairs so that, for example, slide 623 is exposed to anti-human Ig antibody and then developing reagents while slide 643 is exposed to anti-human IgG antibody and then developing reagents. In a third format, a single sample can be analyzed for many antigens if antibodies to these antigens are pre-bound as spots in a known pattern on strips 623 and 643. In a fourth format, specific nucleic acid sequences are spotted at defined loci on the strips 623 and 643 for hybridization assays with prepared samples, such as those wherein sample nucleic acid has been exposed, labeled and placed in suitable hybridization media for

denaturation and hybridization. Such fourth format can also be used for nucleic acid sandwich assays.

This disclosure does not support the examiner's allegation that one of ordinary skill in the art would have been motivated to use the physical separation, i.e., empty space, disclosed in Brigati with the arrays in Southern for the benefit of comparative analysis of the multiple arrays to different samples as provided by the instant invention. In this portion of Brigati, the patent merely states that the same spot on the slides can be tested with different antibodies at the same time, i.e., one sample can be tested for having different antibodies **against the same antigen spot** on the slide. Nothing in Brigati suggests, however, that antigens on different slides can be tested simultaneously against different samples. In other words, even if different antibodies are tested against antigens in the Brigati arrangement, both slides are tested against the same sample at the same time.

The disclosure of Augenlicht also fails to support the examiner's position. Even if Augenlicht teaches multiple arrays on a support separated by a physical barrier i.e. spacing between membranes (Augenlicht at Fig. 1), nothing in the disclosure teaches or suggests that the spaced filters can be assayed against different samples at the same time. The disclosure appears to teach nothing more than what is described in Southern, i.e., multiple filters whether having identical polynucleotides immobilized thereon, as in Southern or different polynucleotides attached as in Augenlicht are simultaneously assayed against the same sample.

The applicant submits that the instant invention provides an advantage over the art, i.e., the ability to carry out a large number of assays at the same time in individual arrays separated by physical barriers or hydrophobic surfaces, and that no combination of the cited art teaches or suggests this invention. While the invention is remarkable in its simplicity, the fact remains that the present application is the first disclosure of this type of system which significantly increases the capacity for data output. Thus, even if the examiner feels that a *prima facie* basis for obviousness has been established (and the applicant does not believe that such a case has been made), this unexpected advantage should be a secondary consideration that leads to a finding of patentability.

The applicant submits that this property, allowing for a heretofore unattainable amount of data accumulation, is taught in the specification to be as a significant advancement

in the art, **but this advantage is not required to be recited in the claims.** To require the claims to recite an unexpected advantage is impractical. Consider, for example, what type of claim language could even be drafted to recite secondary consideration for non-obviousness such as commercial success, long-felt need or failure by others.

Accordingly, the applicant submits that the combined disclosures of Southern and Brigati and/or Augenlicht do not support the examiner's position and, alternatively, even if they did, the advantage over the art that the present invention provides must lead to a finding of patentability.

The second rejection under 35 USC 103(a)

Beginning at page 7, the examiner set out a new grounds for rejection with respect to claims 97, 157 and 175 under 35 U.S.C. 103(a) as being directed to subject matter allegedly unpatentable over the disclosure of Drmanac et al (Electrophoresis, 1992, 13:566-573, hereinafter "Drmanac") and Hardy et al (U.S. Patent No. 4,681,853, hereinafter "Hardy"). Specifically, the examiner asserted the following.

Regarding Claims 97, 157-158 and 166-168, Drmanac discloses a support comprising multiple microarrays (Fig. 4), each comprising an array of differing oligonucleotides immobilized thereon wherein the microarrays are separated from each other. The arrays illustrated in Fig. 4 clearly appear to be separated by a barrier, and the reference teaches that hybridization with different samples requires separation (page 571, last paragraph). The reference does not specifically teach physical barriers. However, physical barriers grooved and/or hydrophobic were well known in the hybridization art at the time the invention was made as taught by Hardy (Fig. 1).

Hardy teaches a similar support comprising a plurality of arrays, each comprising differing oligonucleotides (Column 4, lines 17-56) wherein the arrays are separated by a physical groove and/or hydrophobic strip (Column 4, lines 39-56) whereby hazardous and/or costly materials are handled safely and efficiently (Column 4, lines 10-16).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the physical separation of Hardy to the multiple arrays of Drmanac. One of ordinary skill in the art would have been motivated to do so,

with a reasonable expectation of success, for the expected benefit of providing for safe and efficient handling of hazardous and costly materials as desired in the art (Hardy, Column 4, lines 10-16).

The applicant disagrees. The disclosures cited by the examiner are deficient for the same reasons that the first rejection under 103 cannot be sustained, i.e., nothing in the references individually or in combination suggests that multiple and distinct reactions can be carried out in distinct arrays separated by physical barriers or hydrophobic strips.

Regarding Figure 4 in Drmanac, the legend reads:

Figure 4. Filters with high density dots. The top filter contains 13 824 dots. Bromphenol Blue is added to 2 X YT medium to visualize dots. The array in the middle was obtained by hybridizing the probe ACGACGGCCA complementary to the M13 vector to a filter containing 3456 dots generated by 36 offset prints of M 13 samples from 96-well plates. Empty boxes represents wells without phages or with a deleted vector. Dots in black boxes contain 2- to 3-fold more DNA (higher copy number or more efficient transfer by the particular pins). The array on the bottom is an enlarged part of the middle array. The pins used were 0.5 mm except for the first row of the example on the top and the fourth row of the second example. These dots were made by 0.4 mm pins.

Whether this figure shows that individual arrays "appear to be separated by a barrier" as asserted by the examiner, and the applicant submits that there is absolutely no basis for this assertion, the bottom line is that the reference does not specifically teach physical barriers as admitted by the examiner.

In fact, the disclosure of Drmanac is similar to that of the Southern disclosure cited in the rejection above in that multiple arrays are capable of being hybridized only to the same, single test sample.

For example, at page 571, Drmanac states:

Technically, the hybridization step is performed in two modes. In one, only 1 mL of buffer is used per 8 X 12 cm membrane, which requires covering the filter with a plastic sheet [14]. In an easier mode, 20 mL of buffer is used per filter without covering and shaking, but inconvenient amounts of

radioactivity are necessary for unstable probes. The most difficult and time-consuming step is the washing of the filters.

This disclosure completely discounts the examiner's assertion as to what Figure 4 "appears" to teach. Even if the individual arrays are physically separated, they are not separated to the extent that each array is, or can be, assayed against a different sample in parallel analyses. Either 1 mL of the same test buffer sample or 20 mL of the same test buffer sample is used in the single hybridization reaction against all immobilized probes. The reference simply fails to indicate that distinct hybridization reactions can be carried out with different probes on the support.

The disclosure of Hardy fails to correct this deficiency in the Drmanac disclosure.

Regarding Fig. 1 to which the examiner refers as teaching "physical barriers grooved and/or hydrophobic,"¹ Hardy provides the following description:

In FIG. 1, four clamping assemblies 34 are shown; however, in alternate embodiments of the invention, fewer clamping assemblies 34 could be used. For example, a pair of clamping assemblies 34 on opposing sides of perfusion slit chamber 10 with clamping posts 36 mounted, for example, on opposing corners of cover plates 12, 14 could satisfactorily close and hold cover plates 12, 14 together.

In the preferred embodiment, perfusion slit chamber 10 includes a plurality of heat exchanger fins 46 on each of first and second cover plates 12, 14. Heat exchanger fins 46 are arranged to extend outward of treatment chamber 16 from cover plates 12, 14 and are conveniently molded or machined from the same piece of material used to construct first and second cover plates 12, 14. The particular arrangement of heat exchanger fins 46 shown in FIG. 1 is convenient, but other arrangements will be apparent to those skilled in the art. The function of heat exchanger fins 46 is to strengthen first and second cover plates 12, 14 while simultaneously allowing rapid equilibrium of the temperature of treatment chamber 16 with the ambient.

¹ According to the examiner, "The [Drmanac] reference does not specifically teach physical barriers. However, physical barriers grooved and/or hydrophobic were well known in the hybridization art at the time the invention was made as taught by Hardy (Fig. 1)." Office Action at page 8.

It is unclear where in this figure legend that the examiner finds any basis for asserting that grooved or hydrophobic barriers are taught.

Regarding Column 4, lines 17-56 in Hardy, which the examiner asserts "teaches a similar support comprising a plurality of arrays, each comprising differing oligonucleotides (Column 4, lines 17-56) wherein the arrays are separated by a physical groove and/or hydrophobic strip (Column 4, lines 39-56)," Hardy actually discloses the following.

The apparatus and method of the present invention can be used for a wide variety of types of filters and membranes, including both nitrocellulose and nylon based filters, some impregnated with various substances and resins. The apparatus and method of the invention can conveniently be used with a wide variety of analytical techniques, including, but not limited to, DNA hybridization techniques, DNARNA hybridization techniques, autoradiographic techniques, the southern blot technique used with DNA electrophoresis, the northern blot technique used with RNA electrophoresis, and the western blot technique used in immunoassay of proteins. In addition, the apparatus and method provide a convenient technology for genetic disease screening, especially of the type termed "Restriction Fragment Length Polymorphism" (RFLP). RFLP assays are currently being used for detection of Huntingtons Chorea, sickle cell disease, and other diseases. RFLP assays are also being devised as prenatal screening tests, e.g., Tay Sachs disease, phenylketonuria, galactosemia, sex determination, and other factors.

The preferred apparatus according to the invention can be principally manufactured from plexiglass or polysulfone; such plastics are readily machinable and/or moldable, readily withstand the often elevated temperatures required for incubation and reaction, do not interact with any presently used or known reagents for analyzing filter-bound samples, and do not readily adsorb DNA, RNA, or protein. Other plastics having similar properties may be utilized as necessary. For example, silicon rubber is conveniently used for the required O-rings and gaskets, and the valve assemblies can be fabricated using Delrin. The preferred apparatus of the present invention incorporates no metal parts which might react with the reagents used. Such reactions are to be avoided since corroded metal parts interfere with the operation of the apparatus and use of the method; leached metals can also cause degradation of the reagents and samples of interests.

(Column 4, lines 17-56)

The last paragraph reproduced above is column 4, lines 39-56, to which the examiner specifically points for the purported disclosure that "arrays are separated by a physical groove and/or hydrophobic strip." However, nothing in this cited passage refers to a groove or a hydrophobic surface.

First, the term "hydrophobic" is not found in the Hardy disclosure at all. If, however, the examiner is referring to the silicon O-ring gasket as the hydrophobic component of the Hardy device, reference to Figure 2 shows that the O-ring gasket (numbered 50 in the drawing²) is a barrier that apparently keeps a sample in the confines of the device and does not separate any individual arrays.

With regard to disclosure in Hardy of a "groove," this term is used only in the following instances in the Hardy disclosure:

- Col 7, lines 16-22: As also shown in FIG. 2, the preferred perfusion slit chamber 10 includes a sealing O-ring 50 set into an O-ring groove 52 in a known to those skilled in the art. In the preferred perfusion slit chamber 10, O-ring groove 52 is inscribed into one of cover plates 12, 14; in alternate embodiments, an analogous O-ring groove 52 could be inscribed into each of cover plates 12, 14.
- Col 8, lines 49-52: For manufacturing convenience, it is desirable to construct cover plates 12, 14 identically except for baffles 54, slots 56, O-ring groove 52, and reagent ports 18, 20.
- Col 9, 25-28: body 104 is generally cylindrical and, in the preferred embodiment, grooved around its circumference to accommodate O-rings 110 in a manner well known to those skilled in the art.

In each of these instances, the groove is to secure the O-ring gasket, and like the O-ring gasket, the groove does not separate any individual arrays.

The applicants submits that the combined disclosures of Drmanac and Hardy simply teach that all oligonucleotides on a single support are positioned such that that allow

² Although cover plates 12, 14 are sealingly engaged with O-ring 50 in the preferred embodiment, in alternate embodiments, other types of sealing gaskets and arrangements could be used. Col. 8, lines 16-18.

for testing against only against a single sample, i.e., the probes in each arrangement are not separated by physical barriers or hydrophobic grooves that permit use of different test samples at the same time. As with the first rejection set out by the examiner, a *prima facie* case of obviousness has not been established, and even if it were, the advantage over the art provided by the instant invention must lead to a finding of patentability.

Conclusion

Because (i) the disclosure of Southern in view of either the disclosures of Brigati or Augenlicht and (ii) the disclosure of Drmanac in view of the disclosure of Hardy fails to suggest separation of individual arrays in an apparatus, neither of these combinations can render obvious the invention as claimed. Moreover, because the invention as claimed provides a previously unrealized advantage over the art in that it permits accumulation of unprecedented amount of data, this secondary consideration must point to a finding of non-obviousness even if the examiner had establish a *prima facie* rejection.

Accordingly, the applicant submits that both rejections of claims under section 103 cannot be sustained and both must be withdrawn.

CONCLUSION

In view of the remarks made herein the applicant submits that all claims are now in condition for allowance and request expedited notification of the same.

Dated: October 20, 2009

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